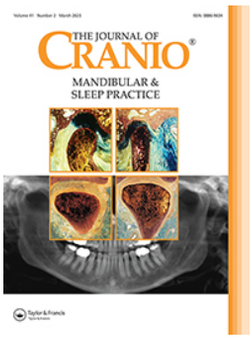

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CASE REPORT

Lacosamide in trigeminal neuralgia: report of a case refractory to first- and second-generation anticonvulsants

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ABSTRACT

Background: The treatment of trigeminal neuralgia (TN) involves first- and second-generation anticonvulsants. However, side effects (SEs) impair compliance with treatment, especially in elderly patients. Lacosamide (LCM) is a third-generation anticonvulsant with a mechanism of action that is not completely clear. It has few SEs and has been considered in the treatment of neuropathic pain.
Clinical Presentation: LCM was prescribed as a monotherapy for a 60-year-old female with TN who had proven refractory to previous treatments in terms of both the absence of any pain relief and the appearance of severe leukopenia. The treatment dosage was 100 mg twice daily. Pain relief was obtained after three weeks of treatment without any SEs. Currently, the patient takes a maintenance dosage of 100 mg/daily, remaining in a state of complete well-being.
Conclusion: LCM has shown evidence of a potential efficacy and a good safety profile in the treatment of this patient with TN.

KEYWORDS
Trigeminal neuralgia; lacosamide; leukopenia; side effects; facial pain

Introduction

Trigeminal neuralgia (TN) is one of the worst types of neuropathic facial pain encountered by clinicians, manifesting as a unilateral, transient, severe, and shock-like pain in facial regions innervated by the trigeminal nerve. Furthermore, the severe and repetitive pain episodes over time can cause disabling and debilitating effects, significantly reducing the quality of life of the patient [1]. Currently, pharmacological treatment is performed with first- and second-generation anticonvulsants. However, these can be ineffective or can cause several side effects (SEs), particularly in the elderly population, which is generally affected [2].

Carbamazepine, a first-generation anticonvulsant, is still considered the gold standard for the initial medical treatment of TN, with a strong level of evidence. Unfortunately, SEs, such as drowsiness, nausea, tremor, dizziness, and hyponatremia, have frequently been reported with the use of this drug.

Potentially serious but uncommon SEs are myelosuppression and aplastic anemia [3].

Lacosamide (LCM) is a third-generation anticonvulsant drug with a good safety profile and with a mechanism of action that is not yet completely clear. It is generally used in the treatment of epilepsy but has also come into consideration as a treatment for neuropathic pain [4].

The present study reports a case of a patient with TN refractory to treatment with conventional anticonvulsants in terms of efficacy and due to the occurrence of severe leukopenia. In this case, LCM has been effective without any SEs.

Carbamazepine is considered the gold standard for the initial medical treatment of TN.

Clinical presentation

A 60-year-old female patient was referred to the Oral Medicine Unit of the University Hospital of Federico II of Naples in October 2016 due to an acute exacerbation of TN, diagnosed two years earlier by the Neurology Unit of the same University, where several anticonvulsant medications were previously tried, but none were effective in controlling the pain without causing SEs.

In the first consultation, the patient reported a worsening of the pain during the previous six months. The patient's pain was described as recurrent and severe, characterized by paroxysms of a strong stabbing nature, electric shock-like, extending in the sensory distribution of the right maxillary and mandibular trigeminal area. The pain lasted only for seconds, occurring over intervals of a few minutes, and was triggered by talking, eating, and touching the affected area, without any autonomic or other neurological symptoms.

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The patient's past medical history was positive for hypercholesterolemia and, therefore, a statin had been prescribed to control the levels of cholesterol.

Previous treatments included gabapentin (up to 1,800 mg/daily), carbamazepine (up to 400 mg/daily), lamotrigine (100 mg/daily), and pregabalin (150 mg/daily). This dosage of the drugs did not control the pain and could not be increased due to the onset of hematological SEs. From the analysis of previous routine blood tests (RBT), it was concluded that the prescription of every one of these drugs was associated with leukopenia [the white blood cell (WBC) count was decreased to 1,900 cells/μL], which was fully reversible after the treatment had been discontinued. Therefore, before any new treatment protocol was initiated, RBT, including complete blood count, glucose, electrolyte, blood urea nitrogen and creatinine levels, and erythrocyte sedimentation rate was requested, in addition to an ECG evaluation. All results proved to be within normal limits.

Magnetic resonance imaging (MRI) of the brain and brainstem with and without intravenous paramagnetic contrast was performed and proved to be normal, except for a few subcortical white matter hyperintensities on the T2 weighted images.

An orofacial evaluation to exclude any dental cause of the pain and a neurological examination was carried out and proven to be normal. Therefore, a diagnosis of TN of the maxillary and mandibular branches of the right side was made.

Three validated scales were administered to the patient for an assessment of pain intensity and an evaluation of the psychological profile:

- the Visual Analogic Scale (VAS) to measure the pain intensity, with a total patient score of 9
- the Hamilton Depression Rating Scale (HAM-D) to assess the severity of depressive symptoms, with a total patient score of 11
- the Hamilton Anxiety Rating Scale (HAM-A) to assess the severity of anxiety symptoms, with a total patient score of 12.

A low dosage of oxcarbazepine (300 mg/daily) was prescribed as a first treatment. After one month, the patient was re-evaluated, and RBT were performed. The WBC count had decreased from 5,500 to 1,900 cells/μL, but no change in the scores of the evaluating scales was revealed.

It was decided to wait until the WBC had returned to a normal level, approximately one month, before starting treatment with LCM. Initially, a dosage of 100 mg during the first week was prescribed, increasing to 200 mg (100 mg/twice a day) during the second week. RBT were requested every week for the first month, and the WBC count had remained within normal limits. After three weeks, the patient reported a state of complete well-being without any pain (VAS score: 0), while no changes in the scores of the HAM-D or HAM-A were found.

Analyses of safety data (SEs, clinical laboratory evaluations, ECGs, vital signs, and physical and neurological examinations) did not reveal any clinically-relevant safety issues. There were no clinical SEs or ECG changes of clinical concern (an absence of QTC prolongation).

RBT were requested and analyzed every month for the first six months, which evidenced that there had been no changes in the WBC test values. After six months, the dosage of the drug was reduced to 100 mg because the patient continued to be in a state of well-being without any pain (VAS score: 0), and the WBC count was normal with an improvement in the scores of HAM-D and HAM-A (to 7). Subsequently, RBT were repeated every four months, and no other SEs had occurred.

Every six months, an additional ECG evaluation was performed. After one year, the dosage was further reduced to 50 mg/daily but, due to a relapse of the pain (VAS score: 4), it was subsequently increased again to 100 mg/daily. Currently, the patient is pain-free and has continued, for the last three years, to take LCM at a dosage of 100 mg/daily without any SEs. Over the years, attempts have been made to apply a reduction in the dosage of the drug. However, due to the relapse of pain, the patient has preferred to continue with a dosage of 100 mg/daily, being monitored every six months.

Discussion

Current evidence-based treatment guidelines suggest the use of first- and second-generation antiepileptic drugs in the management of TN [2]. Carbamazepine and oxcarbazepine have been recommended as a first-line treatment, while an add-on therapy with lamotrigine or a switch to lamotrigine or baclofen has been suggested as a second line treatment [5]. Other antiepileptic drugs, such as gabapentin, pregabalin, topiramate, and levetiracetam have been prescribed in unresponsive cases [2,5].

In the last few years, novel third-generation antiepileptic drugs, such as eslicarbazepine and LCM have been considered for the off-label treatment of neuropathic pain, mainly in refractory cases of TN [6,7].

LCM may offer a better tolerability, in terms of a reduced number of SEs, fewer drug interactions, and a linear pharmacokinetics with predictable blood concentrations, compared to conventional drugs, especially

when used at lower dosages, such as in the treatment of chronic neuropathic pain [8,9]. Therefore, current guidelines suggest that therapeutic drug monitoring of this drug may not be necessary [10].

The advantages of treatment with LCM are summarized in Table 1. The most common, dose-related SEs reported are dizziness, headache, nausea, asthenia, and a slight increase in the PR interval at ECG [3]. Therefore, LCM has been associated with cardiac arrhythmias and atrioventricular blocks, mainly in patients with other cardiovascular risk factors and at a higher dosage (600 mg/daily) [11]. Conversely, it has shown a good tolerability at the approved dosage range of 200–400 mg/daily [12].

In this study, the choice of an off-label treatment with LCM was related to the occurrence of leukopenia associated with previous treatments with conventional drugs. This SE has never been reported with LCM in the literature. The patient in the current study did not report any SEs to the treatment, probably because the dosage considered in previous studies has generally been 400 mg/day, while in this case, half that dosage was prescribed.

The mechanism of action of LCM is multimodal but not yet completely clear. It has shown a neuroprotective action because it inhibits repetitive neuronal firing, stabilizing hyperexcitable neuronal membranes through a mechanism that involves the blocking of voltage-gated sodium channels (VGSC) in a different way compared with that of other antiepileptics [13]. Thus, LCM possesses unique properties demonstrated in vitro and in animal models [14].

In the past, the activity of the drug seemed to be related to the reduction of excessive nerve activities by selectively enhancing the slow inactivated voltage-gate sodium channels (VGSC), both in the peripheral (Na_v 1.7 and Na_v 1.3) and central (Na_v 1.6) nervous system, not mediated by actions at the major excitatory (AMPA/NMDA) or inhibitory (GABA A) postsynaptic receptors with no effects on the fast inactivation. This mechanism of action differs from that of conventional drugs that work predominantly on fast inactivation, leading to a stabilization of the hyperexcitable neuronal membranes and an inhibition of neuronal firing 13–15]. LCM slowly inactivates the channel by rearranging the poor inner structure, preventing the channel from opening, and helping to end the potential action. Instead, conventional drugs, such as carbamazepine, cause a fast inactivation of the channel through an intracellular peptide loop [16,17]. Recent studies, instead, suggest that LCM binds to fast-inactivated VGSC (Na_v 1.7) with slower kinetics than classic antiepileptic drugs [18].

The effect of LCM and classic anticonvulsants on VGSC are summarized in Figure 1 and Table 1.

LCM also seems to modulate the neurotrophic signals mediated by the collapsing response mediator protein 2 (CRMP-2), including Na_v 1.7 expression, neuronal differentiation, polarization, and axonal outgrowth [19].

Finally, LCM shows some anxiolytic/antidepressant effects in patients with epilepsy with comorbid anxious/depressive symptoms, suggesting the possibility of testing this in cases of neuropathic pain, in which an increase in pain perception is related to the vulnerability of the patient [20].

The results of this case reveal that LCM monotherapy is effective in attenuating the pain of TN, indicated by the reduction in pain intensity (VAS score of 0) and by the increasing number of pain-free days, which was evident from an analysis of the patient's pain diary. Other clinical benefits consist of the remission of anxiety and depression, evidenced by the HAM-D and HAM-A scores of 7 after the treatment.

This case shows that LCM significantly decreases pain with a positive effect on mood. This finding is in line with the literature that has shown the utility in psychiatry of antiepileptic drugs as mood stabilizers due to their membrane stabilizing and anti-kindling effects [21]. Therefore, it can be considered an effective and well-tolerated treatment of neuropathic pain, particularly in cases where the patient has reported adverse SEs as a result of treatment with common antiepileptic drugs. Moreover, in recent papers, LCM has shown a greater neuroprotective activity in animal and human studies of painful diabetic neuropathy and painful oxaliplatin peripheral neuropathy compared with oxcarbazepine [22]. No specific signs of abuse potential in LCM treatment have been identified at therapeutic dosage. Conversely, a supratherapeutic dose of 800 mg can cause a euphoric mood and drug dependence [23].

To the best of the authors' knowledge, this is the first well-documented case of a patient with severe leukopenia induced by previous treatment with common

Table 1. Mechanism of action and advantages of treatment with LCM.

Mechanism of Action
Enhancing slow inactivation of VGSC
Peripheral (Nav 1.7 and Nav 1.3) and Central (Nav 1.7)
Stabilization of hyperexcitable neuronal membranes
Inhibition of neuronal firing
Binds CRMP-2 changes in axonal outgrowth
Advantages of treatment
Excellent oral bioavailability
Minimal serum protein binding
Excreted unchanged in the urine
Drug-drug interactions are minimal

LCM: Lacosamide; VGSC: Voltage-gate sodium channels; CRMP-2: Collapsing response mediator protein 2

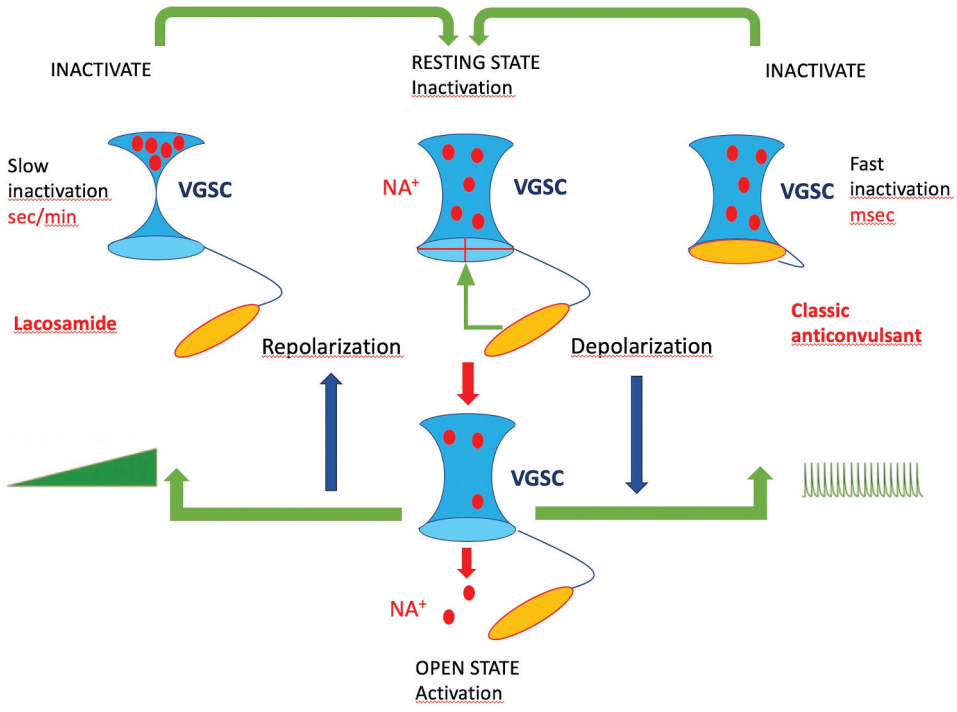

Figure 1. Understanding the mechanism of action of LCM and classic anticonvulsant on VGSC: LCM enhances slow inactivation of VGSC, while classic anticonvulsant enhances fast inactivation of VGSC. Slow inactivation of VGSC involves rearrangement of the inner pore structure, while fast inactivation is mediated by an intracellular peptide loop located between domains III and IV. LCM: Lacosamide; VGSC: Voltage-gated sodium channel.

anticonvulsants for TN showing positive results after monotherapy with LCM.

Limitations

The results of the study are encouraging, but there are several limitations, principally, that this is a single case report. The effectiveness of the treatment is exploratory and should be interpreted with care. Further case-control and randomized studies are necessary to determine the efficacy of LCM as a viable treatment protocol for patients with TN.

Conclusion

LCM shows potential efficacy, good safety profile, fewer drug interactions, and milder SEs, compared to the older generation of anticonvulsants in the treatment of this patient with TN. This off-label treatment could be considered when other treatments have failed or caused intolerable SEs.

Acknowledgments

Dr. D.A. designed the treatment protocol and wrote the article. Dr. N.C. designed and edited the figures and tables. Prof. M.N. and M.M. evaluated the patient and edited the final version of the article. All of the authors have read the final version of the manuscript and approved its content.

Consent

Written informed consent was given by the patient for the publication of this case report and the accompanying images.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Disclosure statement

The authors declare that there are no conflicts of interest regarding the publication of this article.

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